HFD-613/OGD

NDA 17-970/S-040

OCT 2 9 1998

Zeneca Pharmaceuticals
Attention: W. J. Kennedy, Ph.D.
Vice President, Drug Regulatory Affairs
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Dr. Kennedy:

Please refer to your supplemental new drug application dated April 30, 1998, received April 30, 1998, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nolvadex (tamoxifen citrate) Tablets.

We acknowledge receipt of your submissions dated May 7; June 18, 24, and 25; July 1, 2, 16, 17, 20, 21, 27, 29, and 31; August 4, 7, 10, 12, 19, 20, 21, 26, and 27; September 17, 23, 25 and 28; October 5, 13, 15,20,2 1,22, and 23, 1998. The user fee goal date for this application is October 3 1, 1998.

This supplemental new drug application provides for the use of Nolvadex (tamoxifen citrate) Tablets, to reduce the incidence of breast cancer in women at high risk for breast cancer.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 17-970/S-040." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated October 20, 1998. These commitments, along with any completion dates agreed upon, are listed below.

1. Thromboembolic events are a significant risk for women taking tamoxifen. As discussed at Oncologic Drugs Advisory Committee and recommended by the Committee, you should perform a study to evaluate the etiology of drug-related clotting events, including assays for Factor V Leiden and activated protein C resistance. The study protocol should be submitted for review prior to initiation.

2. All participants on the NSABP P-l trial should have long-term follow-up for the events of cancer (invasive breast, non-invasive breast, endometrial, and other cancer), death, stroke, deep vein thrombosis, and pulmonary embolism. Data should be submitted at least yearly.

3. Data from the following P-l substudies should be submitted when available:

   - NSABP P-lB, "Bone mineral density and biochemical marker study to determine the effect of tamoxifen on bone in premenopausal and postmenopausal women"
   - NSABP P-lG, "A study of the association between inherited mutations and the effect of tamoxifen on breast cancer incidence"
   - Dr. Krag's substudy, "The effect of tarnoxifen on the hemostasis system in women without breast cancer: Implications for cardiovascular disease prevention and assessment of thrombotic risk"

   A timetable for submission should be provided.

4. Provide the results of the ongoing NSABP central pathology review, to include tumor grade as well as any other analyses you perform. These results can be provided on a rolling basis by category (for example, breast cancers, endometrial cancers, etc.). Provide the anticipated timetable for submission.

5. Please submit all relevant draft manuscripts for the NSABP P-l trial when available, prior to submission for peer review.

All Phase 4 studies that may impact the labeling of tamoxifen should be submitted to the Division of Oncology Drug Products and reviewed prior to initiation.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondence. In addition,

under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

The set of slide rules used to calculate the 5-year absolute risk of breast cancer, using the Gail Model, is considered part of the approved product labeling. Because it is not practical to distribute these tools with all product shipments and promotional materials, FDA will not require that the slide rules be attached to every Nolvadex package insert, patient package insert or to the promotional materials. However, Zeneca must maintain a l-800 number listed in the label dedicated to processing requests for the Gail Model Risk Assessment Tools in a rapid and efficient manner. The number must not be used for promotional information, adverse event reporting, etc.

We understand that Zeneca also intends to make the Gail Model available on a computer disk in the future. The computer disk form of the Gail Model will also be part of the approved product labeling and must be approved as a labeling supplement to the NDA prior to distribution. FDA will review the labeling supplement for addition of the computer disk to the approved product labeling on an expedited basis.

Please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Oncology Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
F D A
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.